# ACTH-dependent severe hypercortisolaemia treated with osilodrostat and etomidate combination therapy- a case report

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## Introduction

Severe hypercortisolaemia (SH) is a life-threatening condition defined as a significantly elevated random serum cortisol level (>36-41 µg/dL), 24-hour urinary free cortisol (UFC) level higher than four-fold the upper limit and/or severe hypokalaemia (<3.0mmol/L). Normalization of cortisol production is crucial in case of SH, however, achieving control can be challenging with standard anticortisolic therapy. The effectiveness of SH management can be increased by a dual blockade of cortisol production. We report a 32-year-old female with ACTH-dependent SH brought into control through combined therapy of two steroidogenesis inhibitors: etomidate and osilodrostat, and then maintaining a stable cortisol level with osilodrostat monotherapy.

## Case description

A 32-year-old female was admitted to the Department of Internal Medicine, Endocrinology and Diabetes due to general condition deterioration, polydipsia, polyuria, qualitative disturbance of consciousness and severe hypokalaemia (1.9 mmol/L). For about 2 months before the admission, facial hair growth, acne lesions, a tendency to bruise and secondary amenorrhea had been observed. Physical examination revealed high blood pressure (155/100 mmHg), moon face with acne lesions and limb muscular atrophy. BMI was 22.4 kg/m$^2$. The initial laboratory tests showed hyperglycaemia (202 mg/dL) and metabolic alkalosis with profound hypokalemia (2.2 mmol/L). Oral hypoglycaemic drugs were introduced along with aggressive hypokalaemia repletion and antihypertensive treatment. Despite intravenous and oral potassium supplementation, it was not possible to normalize the kalaemia. Given the overall clinical presentation and resistance to initiated treatment, hormonal diagnostics was extended and the patient was diagnosed with ACTH-dependent SH. The hormonal findings are summarized in Table 1.

| Parameter | Value |
|---|---|
| Midnight serum cortisol (µg/dL) | 64.69 (N: < 5.4) |
| Morning serum cortisol (µg/dL) | 106.0 (N: 3.7 – 19.4) |
| Urinary free cortisol (µg/24h) | 7155.0 (N: 4.3 – 176.0) |
| Baseline ACTH (pg/mL) | 167.0 (N: 6.0 – 48.0) |
| ACTH after CRH stimulation test (pg/mL) [Δ] | 0': 154.4; Max: 989.10 [540.61%] |

**Table 1.** The laboratory findings of hypercortisolism.

Initially, therapy with osilodrostat was introduced in increasing doses, improving the patient's general condition during the beginning days of treatment. Then, due to persistent hypokalaemia (despite potassium supplementation and high doses of spironolactone), inefficiency in further decreasing serum cortisol concentration, lower limbs oedema accompanied by deterioration of patient well-being, etomidate infusion was started in a gradually increased dosage simultaneously with osilodrostat. Evolution of serum cortisol and potassium levels during osilodrostat and etomidate treatment are presented in Fig.1 and Fig.2, respectively.

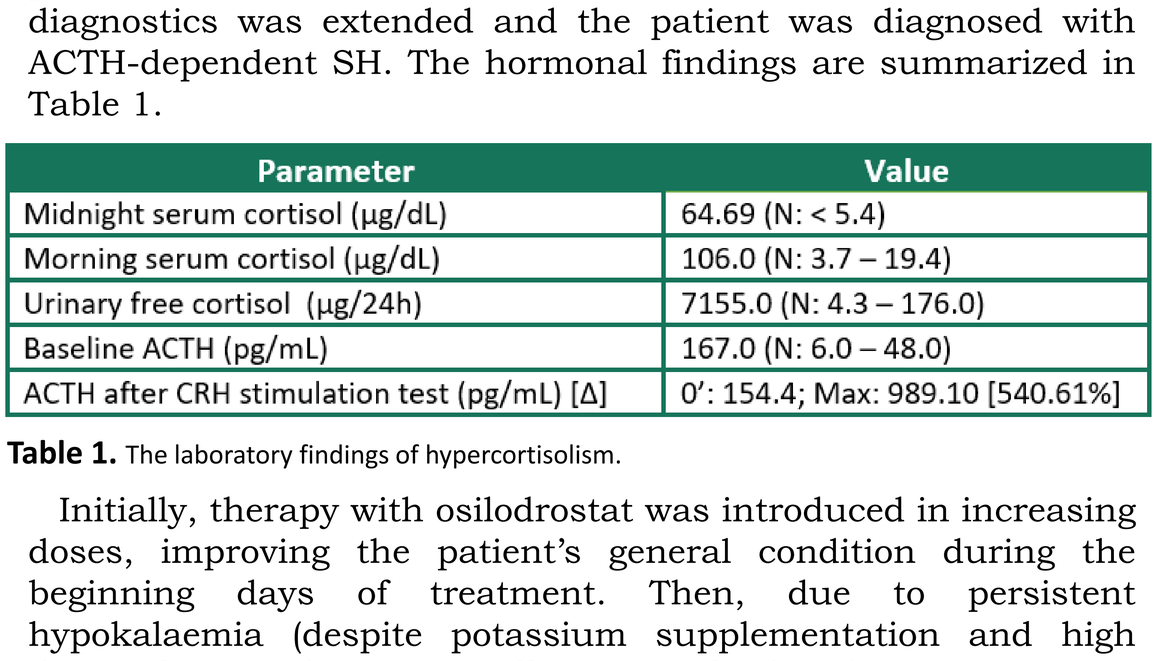


**Fig. 1.** Evolution of serum cortisol concentrations during treatment with osilodrostat and etomidate. Cortisol values are the average of 3-8/day time measurements (depending on the day). The shaded area corresponds to the cortisol reference range.

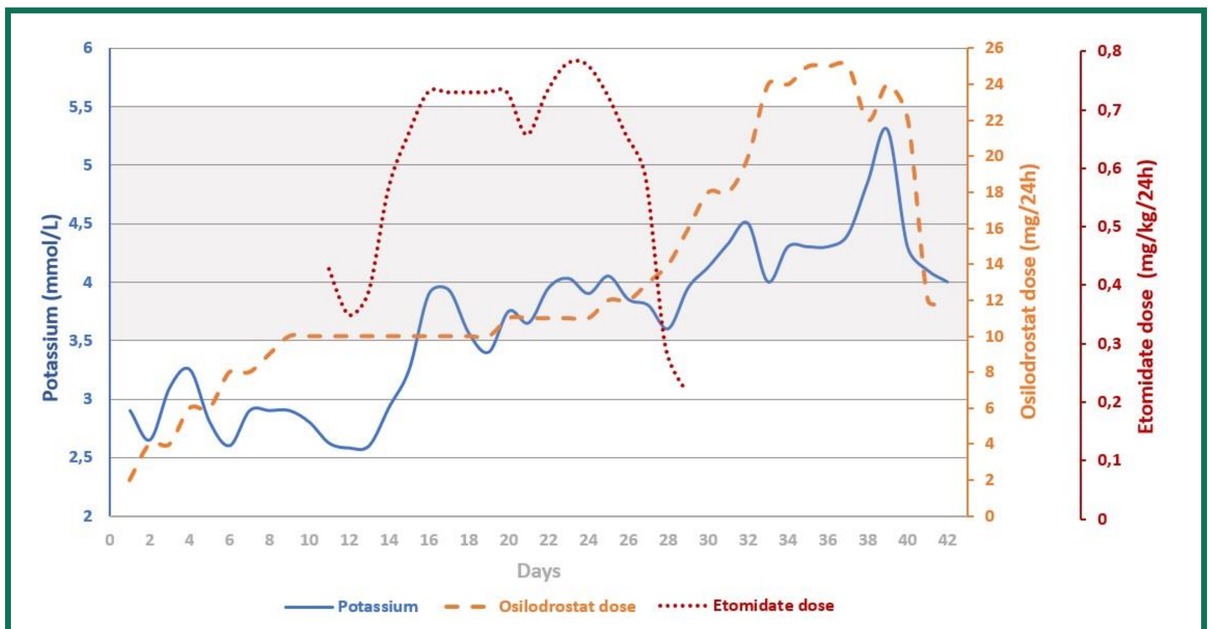


**Fig. 2.** Evolution of potassium concentrations during treatment with the osilodrostat and etomidate. Potassium values are the mean of 1-8/day time measurements (depending on the day). The shaded area corresponds to the potassium reference range.

The doses of etomidate and osilodrostat were adjusted and titrated according to cortisol, potassium, glucose, and blood pressure measurements. The patient tolerated therapy well (no side effects were reported) and improvement in the patient's general condition was observed. After stabilization of cortisol levels and kalaemia, treatment with etomidate was discontinued and osilodrostat was continued in doses adjusted according to the hormonal laboratory evaluations. An MRI of the pituitary gland was performed, in which the inconclusive image as to the presence of microadenoma was visualized (Fig.3). In the opinion of the consulting experienced neurosurgeon, the ambiguous change in the pituitary gland was not the source of the autonomous production of ACTH.

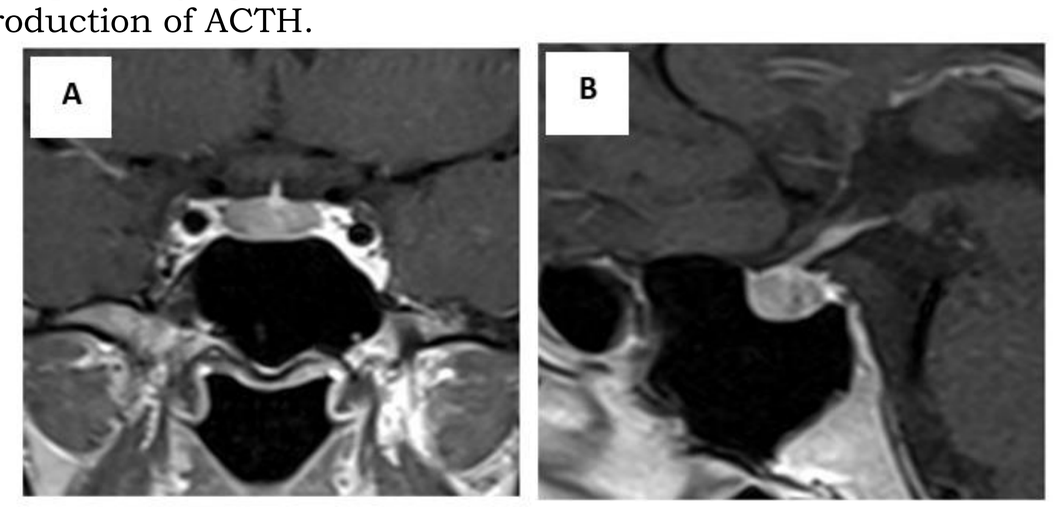


**Fig. 3.** Frontal (A) and sagittal (B) MRI of the pituitary gland of the presented patient without evident signs of microadenoma.

A whole body computed tomography and subsequent 68-Ga-DOTA-TATE-PET/CT did not reveal any abnormalities. The patient was discharged from our Department in good general condition and continuation of osilodrostat with recommended dose of 6 mg bid. The patient is still followed-up in our Clinic.

## Discussion

The treatment of SH remains a challenge as no medication has complete and definitive efficacy in hypercortisolaemia management. The use of individual anticortisolic drugs is also limited by the frequent occurrence of their side effects. Combination therapy with medications of additive, synergistic or/and complementary mechanism in anticortisolic action could increase treatment efficacy and minimize adverse events.

To conclude, we report a case of ACTH-dependent SH successfully treated with a combination of osilodrostat and etomidate. Combined therapy was well tolerated and highly effective in controlling ACTH-dependent SH and provides an alternative to the current therapeutic regimens. This strategy allowed us to reduce the risk of medications side effects and control the level of cortisol with minimized risk of adrenal insufficiency in non-ICU conditions, despite the longer time of hypercortisolaemia normalization. Perhaps, a higher beginning dose of osilodrostat, more rapid dose titration, or earlier etomidate introduction should have been taken into consideration to increase the regimen efficacy, although, it could have required the "block and replace" strategy. Complementary observations are needed to confirm the efficacy and safety of that therapeutic approach in SH management and to establish optimal starting doses and cross-titration strategy of osilodrostat and etomidate.